A new PBTK modelling method based on multi interaction paradigm

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ABSTRACT :

One of the problems not clearly solved nowadays in food toxicology, is the evaluation of internal exposure to natural chemical contaminants. The worst solution is based on the concept that internal and external exposure are of the same level. One can go through this concept by considering biomarkers which can be used to calculate the inner contamination. Another solution is the use of a PBTK simulation method (Physiologically-Based Toxico-Kinetics). This method allows the knowledge of distribution of the contaminant over all the organs and their evolution in time. Unfortunately, the modeling and simulation processes are very hard to implement and use. The use of a technology issued from virtual modeling shows a good opportunity of developing a user interface easy to use for biologists. This interface is based on the multi interactions paradigm which is an evolution of the multi agent simulations.

INTRODUCTION

Food toxicology is a science which is interested in the analysis of bad consequences of eating on health. For new chemical components of food, a toxicological study is made which allows the determination of a usable limit of this chemical in food in order to be sure that no adverse consequences could occur. For natural components, it is impossible to decide in such a way and so a method of evaluation of the internal exposure is needed. For some natural components biomarkers are well known in blood or urine for instance. In those cases, the knowledge of the quantity of biomarkers allows the determination of inner exposure. Unfortunately, for most chemicals no biomarker is known and the only solution is to mathematically calculate that exposure. In order to do this the PBTK modeling and simulation method is considered as the best current solution (US EPA, 2006). However, this method is very difficult to use and few results are obtained because of two main reasons (Krishnan and Andersen, 2008). The first one is that numerous parameters are needed for each chemical and it is not very easy to determine them. The second problem is that this method was developed by computer scientists and mathematicians and need a large mathematical and numerical background to be used in good conditions. If solutions are generally found for the first problem, consisting in the comparisons of the chemical under analysis with other chemicals of the same family for instance, no real progress was made for the second problem, which needs to move from a mathematical paradigm to another one. This last one could be the use of virtuality.

PBTK MODELLING

Pharmacokinetics involves the study of the time course of the parent chemical or metabolite concentrations or amounts in biological fluids, tissues, and excreta and the construction of mathematical models to interpret such data (Wagner, 1981). The time course of the concentration of a chemical or its metabolite in biota is determined by the rate and extent of absorption, distribution, metabolism, and excretion (ADME). The pharmacokinetics or ADME of a substance determines the delivered dose or the amount of chemical available for interaction in the tissues. Relating adverse response observed in biota to an appropriate measure of delivered dose (e.g., concentration of the toxic chemical in the target tissue) rather than administered dose or exposure concentration is likely to improve the characterization of many dose-response relationships.
Adverse tissue responses are more directly and closely

related to the internal target tissue dose of the toxic moiety than to the concentration of the parent chemical in the environment. Therefore, the scientific basis of, and confidence in, risk assessments are enhanced when they are supported by estimates of the internal tissue dose. Data for the internal tissue dose levels, however, are generally not available, and the relationship between external and internal dose may not be easily resolved. PBTK models provide a means of estimating the internal dose for many different exposure regimens based on what is known about the physiology of the test species and the chemical of interest. PBTK models reduce the uncertainty in dose-response and exposure assessment

MULTI INTERACTIONS PARADIGM

A classical PBTK model is a compartment model, each representing organs or group of organs. The flows between compartments represent the veins and arteries. This kind of description can be computed in terms of a multi-agent model. Each organ (or group of organ) being an agent.

In a multi agent model, each agent has three functions: observing his neighborhood, deciding if something has to be done, and applying that decision. Then, for instance, if you model a colony of individuals interacting, each individual is an agent with its own behaviour. This method of modeling has a great advantage in programming because each agent is independent and can have its own functionalities. It is easy to understand the program and to modify it, because all algorithms are simples. The complexity of the global behaviour comes from the multiplication of agents. Classically one has an individual-based vision of the world, or in our area an organ-vision of the human body. That means that the important point is the description of these organs, and then, in order to link these isolated parts, one describes the possible interactions. Then, interactions between two organs have to be described in these two organs.

Anyway, in a PBTK model, what is really important to model is not the state of each organ but the evolution of the chemical concentrations. These concentrations change because of the flows between the compartments. Then the important elements are these flows, which are called interactions in this new paradigm. That is the reason why we propose a multi-interactions model. In this case the main elements to be modeled are the interactions between organs, these last ones being described only through their state changes due to the flows variations (the interactions). A theoretical description of this paradigm can be found in (Desmeulles et al. 2009).

TOXCIN PROGRAM

The ToxCin program is an application of the multi-interactions paradigm to PBTK modelling. In the application of this concept, we use different elements:

−The phenomenon, which can create new interactions when it is justified. The interaction is a specific manifestation of the phenomenon. Interaction is classically called flow.

−The organization is defined as a set of phenomena and interactions. Practically, each one corresponds to one organ.

−The components are compartments corresponding to concentrations, volumes and parameters necessary for simulation.

−The influences are mathematical element allowing the creation of links between two components.

For instance, on fig1, the two biggest rectangles are two organizations representing organs. Inside these elements small rectangles are components corresponding to concentrations of the chemical and volume. The circle inside organization 2 is an interaction representing metabolization in that organ. The circle situated outside the organizations is an interaction representing the flow of chemical betwwen the two organs. All these elements are defined by values and equations such as chosen on fig2

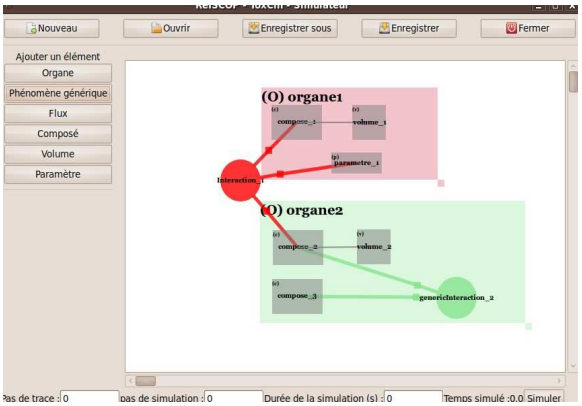

Figure 1: example of a simple model showing two organizations with flow between these ones and a metabolization.

ToxCin was applied on an example of dioxin exposure through inhalation already published (Bois, 2002), in order to evaluate its possibilities and limitations. The model is shown on fig3. Comparisons between the simulation results between the classical PBTK modelling using MATLAB programming, and this new

methods show good agreement. The avantage of Toxcin is its programming simplicity only based on a visual method and not necessitating any knowledge in programming. Anyway at this time there is no help for defining the equations needed or for final visualization of the variations of chemicals concentrations in the organs analysed.

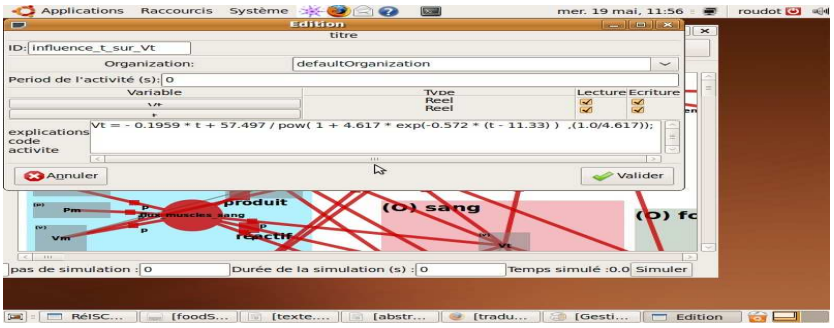

Figure 2: Example of a defining window for an influence in the dioxin model of fig3.

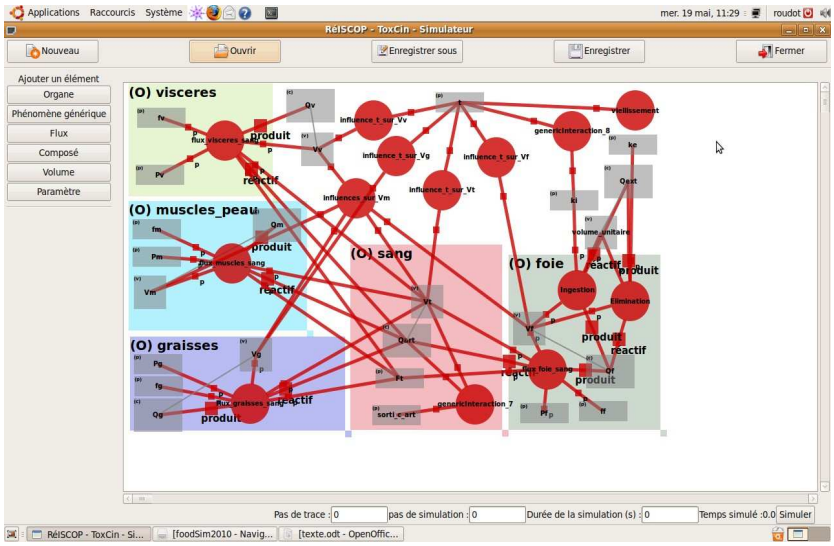

Figure 3: The PBTK model created by ToxCin, concerning the women exposure to dioxins

CONCLUSION

The current model is yet under tests but it can do classical PBTK modeling i.e. calculating the variation of concentrations of chemicals amongst the different organs or in the blood. Its main current interest is the interface which is totally graphical and can be used by everybody after a short-time training (Fig 1 and 3). The only elements to enter are the biological and chemical constants (which could be taken from scientific litterature) and (for the moment) the transfer equations in the interactions and influence. Its further evolutions will be in the possibilities of working together on the chemicals and its metabolites, in adding a method in order to take into account the parameters variabilities and in a better user interface with an help in writing the different mathematical equations, and better results publishing properties.

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